REMARKS

Claims 41-91 were pending in the subject application. Claim 41-48, 51-53, 56-67, 69-71, 73-87 and 90-91 are withdrawn from consideration by the Examiner as directed to non-elected subject matter. By this Amendment, applicant has canceled claims 68, 76, 88 and 89 without prejudice or disclaimer, amended claims 49, 50, 54, 55 and 72, and added new claims 92-93.

Applicant maintains that the claim amendments do not raise an issue of new matter. Support for the claim amendments can be found at least in previous versions of the claims and in paragraph [0080] on page 20 of the application as filed.

The specification has been amended to remove the word "said" from the Abstract and to correct the spelling of pipamperone. Applicant maintains that the amendments to the specification do not raise an issue of new matter.

Entry of the amendments is respectfully requested.

Objection to the Abstract

The Abstract was objected to for reciting the word "said." The Abstract has herein above been amended to delete the word "said," thereby obviating this objection.

Objection to the Disclosure

The disclosure was objected to for misspelling "pipamperone." The disclosure has herein above been amended to correct the spelling of "pipamperone," thereby obviating this objection.

Rejections under 35 U.S.C. §112, First Paragraph

Claims 49, 54, 68, 72 and 88-89 are rejected under 35 U.S.C. §112, first paragraph, as not enabled for the full scope of the claims. The claims have herein above

been amended to recite specific compounds and provide dose amounts. In particular, all the claims under examination now recite that one of the compounds is pipamperone in a dose ranging between 5 and 15 mg of the active ingredient. Accordingly, reconsideration and withdrawal of this ground of rejection are respectfully requested.

Rejections under 35 U.S.C. §112, Second Paragraph

1. Claims 49-50, 54-55, 68, 72 and 88-89 are rejected for reciting "such as." The claims have herein above been amended to remove recitation of "such as," thereby obviating this rejection.

2. Claims 49-50, 54-55, 68, 72 and 88-89 are rejected as directed to "a composition" as "a combined preparation...for separate or sequential use..." The Examiner indicated that a composition cannot be used separately. The claims have herein above been amended to replace "A pharmaceutical composition" with "A pharmaceutical combined preparation," thereby obviating this rejection.

Rejections under 35 U.S.C. §103(a)

1. Claims 49, 54, 68 and 72 are rejected as unpatentable over Steiner et al. (US 6,300,354) in view of Hubble (Eur. J. Neurol. Suppl. 7(Suppl 1): 15-20, 2000) and Silver et al. (Neurology 50(Suppl 6): S18-S22, 1998).

Specifically, the Examiner indicates that Steiner discloses compounds, *i.e.* N-substituted azabicycloheptane derivatives, having high affinity for the D4 and 5HT-2A receptors. However, Steiner does not teach any of the other features of the claims. Indeed, Steiner prefers to use this compound in neuroleptic disease (see claim 2). Secondly, there is no hint or teaching towards combining these compounds with further compounds. Thirdly, Steiner mentions that these compounds have a very high and

selective affinity for the 5HT-2A and D4 receptors (see col. 2, lines 57-59), but does not refer to affinities for other compounds, such as, e.g. the adrenergic α or β or histamine H1 receptors (except for prior art compound A, which has a good selectivity versus D2, col.1, l.16-17). In addition, it is not mentioned whether this compound is an agonist or an antagonist. Moreover, the dosage exceeds the claimed dose (see col.3, l.7-8, oral administration).

According to the Examiner, Hubble teaches the use of the conventional dopamine agonist pergolide in treating Parkinson Disease (PD). However, applicant notes that Hubble mentions that the conventional dopamine agonists have serious side effects. As such, these conventional dopamine agonists are disfavored. To the contrary, the novel dopamine agonist pramipexole in treating PD is advocated. Accordingly, reading Hubble, the skilled artisan would not be prompted to use pergolide.

Moreover, applicant maintains that there would be no motivation to combine any of these documents. Specifically, Hubble mentions explicitly that pramipexole has a high affinity for the D2 receptor family (D_2, D_3, and D_4) but not for the D1 receptor family (D_1 and D_5), while having virtually no other receptor antagonism or agonism. In other words, since pramipexole is favored, it must follow that other receptor antagonism or agonism is dissuaded. Hence, no further compound, in particular an extra antagonist will be administered.

Silver advocates treatment with dopamine ***agonists*** (in general) throughout the article. It is not specified which dopamine receptor should be activated. Hence, the person skilled in the art would not use a dopamine receptor D4 ***antagonist***. Indeed, even when Silver teaches that carbidopa-levodopa is used, it is in combination with a dopamine ***agonist***. The effects of 5HT-2A are not discussed.

In addition to the foregoing, applicant notes that the claim amendments made herein above have limited the claims to pipamperone, which applicant believes obviates this rejection.

Accordingly, reconsideration and withdrawal of this ground of rejection are respectfully requested.

2. Claims 50 and 55 are rejected as unpatentable over Mantelle (US 5,446,070).

According to the Examiner, Mantelle would teach the various combinations of compounds. However, the passages cited by the Examiner merely list the compounds, but do not specify the combination. In column 23, lines 31-36 it is stated that "Indeed, the present invention is intended to encompass and be suitable for use by substituting any of the following ***drugs*** [plural] for the anesthetic agent as the pharmacologically active ***agent*** [singular] in the composition and methods for use of the same." (emphasis added). In other words, no combinations are contemplated. Notwithstanding the above, the specific combination of the present invention has not been taught or suggested. In fact, combining two compounds of the vast list of Mantelle gives over 1 billion combinations. Finding the specifically claimed combination amounts to undue burden.

Secondly, the Examiner argues that Mantelle would teach compositions. However, applicant maintains that Mantelle relates to "bioadhesive composition for topical application", but not to pharmaceutical compositions as such.

Thirdly, the Examiner argues that varying and/or optimizing the quantity of pharmacological agents would be routine. However, optimizing a dose presupposes a purpose. In this case, treating PD. Mantelle does not refer to PD. Mantelle does not teach that the either compound can be used for treating PD, even less that the claimed combination would be particularly beneficial in treating PD. Diagnosing PD is difficult. Indeed, in the section bridging columns 1 and 2 on page S18, Silver (cited by the

Examiner) signifies the same. Finding an appropriate dose presupposes a correct diagnosis of the disorder. In the present case, pipamperone is not recommended for treating PD. Accordingly, a correct diagnosis of PD would avert the use of pipamperone. In addition, all the art points to one direction, *i.e.* using the highest tolerable dose. There is no teaching of lowering a dose (see e.g. the section "Conclusions" on page S21 of Silver). Hence, routine experimentation would be increasing a dose, and observing whether an effect is realized. If no effect is observed, the person skilled in the art will turn to another medicament. In this regard it is to be noted that at least pipamperone is provided in an unconventionally low dose. Moreover, in the present case, the enhanced clinical effect is dependent upon two compounds, which act synergistically. However, at other doses, these compounds have no mutual effect, or even have opposing effects. Indisputably, this adds to the complexity of determining any dose. Thus, determining at which dose pipamperone augments the efficacy of a second compound is certainly not routine, but either goes against the teaching in the art or amounts to undue burden.

Accordingly, reconsideration and withdrawal of this ground of rejection are respectfully requested.

3. Claims 88 and 89 are rejected as unpatentable over Steiner et al, in view of Hubble and Silver et al., in further view of Mantelle, and in further view of Schotte (Psychopharmacology 124:57-73, 1996).

Claims 88 and 89 have been herein above been deleted. As such, this rejection is moot.

Notwithstanding the above, applicant notes that Steiner does not refer to pipamperone. Steiner in view of Hubble and Silver has already been discussed above. Applicant believes that these arguments are also applicable in the present case. Again, no reference is made to pipamperone.

In regard to Steiner in view of Mantelle, even less than either Hubble or Silver, this combination does not refer to PD. When reading both documents, the person skilled in the art would at most be taught that the component of Steiner can be used as a bioadhesive composition for topical application.

Schotte is relates to a comparative study on risperidone. Specifically, risperidone was compared to reference antipsychotic drugs, including pipamperone. It is concluded that "The predominant 5HT-2A receptor occupancy probably plays a role in the beneficial action of risperidone on the negative symptoms of schizophrenia, whereas maintenance of moderate occupancy of D-2 receptors seems adequate for treating the positive symptoms of schizophrenia. A combined 5HT-2A and D-2 occupancy and the avoidance of D-2 receptor overblockade are believed to reduce the risk for extrapyrimidal symptoms." Applicant understands that no reference is made to combining drugs. No teaching or suggestion is made towards using pipamperone in treating PD. No specific relevance is given to D4 antagonism. In fact, the use of pipamperone is dissuaded since it has 2 orders of magnitude lower D-2 affinity than risperidone, which is the preferred compound.

Provisional Obviousness-Type Double Patenting Rejection

Applicant acknowledges the Examiner's provisional rejection of Claims 50 and 55 on the ground of nonstatutory obviousness-type double patenting over claims 1 and 4 of co-pending, later-filed US application 10/984,683, Buntinx (US 2005/0203130).

CONCLUSIONS

In view of the preceding amendments and remarks, applicant respectfully requests that the Examiner reconsider and withdraw the objections and rejections set forth in the May 3, 2007 Office Action, and earnestly solicits allowance of the claims under examination. If there are any minor matters preventing the allowance of the subject application, the Examiner is requested to telephone the undersigned attorney.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required to maintain the pendency of the subject application, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785.

Respectfully submitted,

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By _____
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